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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,470	11/20/2001	Ruey S. Liou	TNX99-05-01	3795

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,470	LIOU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment received on 10/22/03 has been entered. Claims 18 and 20 have been canceled and new claims 24-27 have been added. Claims 17, 19, and 21-27 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 112

The rejection of claims 17-23 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn in view of applicant's cancellation or amendment of the claims, and further in view of applicant's arguments concerning the relevance of the animal model used in the working examples and the state of the art of anti-IgE therapy as evidenced by Corne et al., MacGlashan et al., and Patalano.

The rejection of claims 17-23 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's cancellation or amendment of the claims.

Claim Rejections - 35 USC § 102

The rejection of claims 17-21 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,066,718 (5/23/00), hereafter referred to as Hardman et al., is withdrawn in view of applicant's cancellation or amendment of the claims.

Claim Rejections - 35 USC § 103

The rejection of claims 17 and 23 under 35 U.S.C. 103(a) as being unpatentable over by U.S. Patent No. 6,066,718 (5/23/00), hereafter referred to as Hardman et al., in view of U.S. Patent No. 6,468,547 (10/22/02), hereafter referred to as Buchsbaum et al., is withdrawn in view of new grounds of rejection of the claims under 35 U.S.C. 103 below.

Applicant's amendments to the claims and addition of new claims has resulted in the following new grounds of rejection.

Claims 17, 19, and 21-27 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over by U.S. Patent No. 6,066,718 (5/23/00), hereafter referred to as Hardman et al., in view of Whittington et al. (1998) Gene therapy Vol. 5 (6), 770-777, and U.S. Patent No. 6,468,547 (10/22/02), hereafter referred to as Buchsbaum et al. Applicant's arguments as they pertain to the

new grounds of rejection have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant has amended the claims to recite *in vivo* methods of administering to a patient a composition comprising an adenoviral vector comprising a nucleic acid encoding an anti-IgE antibody or IgE binding fragment thereof. The claims recite that the methods are for producing an IgE antibody, inhibiting the binding of IgE to its high-affinity IgE receptor, or suppressing or attenuating an IgE mediated allergic disease.

Hardman et al. teaches nucleic acids encoding the heavy and light chains of a humanized reshaped monoclonal antibody against IgE based on the TES-C21 antibody, which does not bind to either the high or low affinity receptors and further inhibits the binding of IgE to the IgE receptor (columns 23-31). Hardman et al. also appears to teach an antibody that is equivalent to what the specification refers to as Hu-901. The specification states on page 7 that Hu-901 is described in AU 675449. The AU 675449 patent is in the same patent family as U.S. Patent 6,066,718 and has a similar disclosure. Thus, in the absence of evidence to the contrary, Hardman et al. teaches the Hu-901 antibody and the nucleic acid sequences encoding the Hu-901 antibody. Hardman et al. also teaches vectors encoding said nucleic acids, host cells transformed with said vectors, and methods of producing an anti-IgE antibody by culturing a host cell transformed by said expression vectors (Hardman et al., columns 69-70, claims 1-10). In particular, Hardman et al. teaches that the vectors encoding the anti-IgE antibody utilize strong promoters, and in particular the CMV promoter, to express the encoded antibody (Hardman et

al., column 15, lines 22-41, and column 16, lines 18-28). Hardman et al. also teaches the use of the disclosed antibodies to inhibit IgE (Hardman et al., column 22, lines 15-25, and 63-67). While, Hardman et al. does not specifically teach the use of a nucleic acid encoding an anti-IgE antibody *in vivo*, Hardman et al. does teach that the anti-IgE antibodies encoded by the disclosed nucleic can be used to treat or prevent allergic diseases *in vivo,* and that the therapeutic effect of the antibodies stems from their ability to bind free IgE and inhibit the binding of IgE to the IgE receptors, including the high-affinity IgE receptor (Hardman et al., column 21-22, lines 49-67 and lines 1-25).

Whittington et al. supplements Hardman et al. by teaching the intravenous delivery of an adenoviral vector encoding a single chain antibody *in vivo* resulting in the expression of biologically active levels of the encoded antibody (Whittington et al., pages 771, 773, and 775). Whittington et al. further provides motivation for administering an adenovirus encoding an antibody *in vivo* over the antibody itself by teaching that, "Antibodies and their recombinant fragments have enormous potential for therapy of malignant and other diseases, but there can be problems associated with their production and purification in the quantities required for therapeutic use" which can be overcome by using recombinant nucleic acids to express the antibody *in vivo* (Whittington et al., page 770). Whittington et al. also teaches that an additional advantage to expressing the antibody using a recombinant vector rather than directly administering the antibody is the extended expression of the antibody *in vivo* for longer periods of time without readministration (Whittington et al., page 774, column 1, second paragraph).

Buchsbaum et al. further supplements Hardman et al. and Whittington et al. by teaching the therapeutic use of adenoviral vectors to express single chain antibodies under transcriptional control of the CMV promoter *in vivo* to treat disease (Buchsbaum et al., column 17, lines 14-19). Buchsbaum et al. further provides motivation for the therapeutic administration of an adenovirus encoding a single chain antibody by demonstrating the actual treatment of tumors *in vivo* following administration of an adenovirus encoding a single chain antibody (Buchsbaum et al. columns 16-17, example 3). Buchsbaum et al. also provides specific motivation for using an adenovirus encoding a single chain antibody over a nucleic acid encoding a single chain antibody by teaching that the adenoviral vector encoding the antibody exhibited the highest in situ gene transfer of the tested vectors (Buchsbaum et al., column 23, lines 57-59). Thus, in view of the motivation to use a nucleic acid encoding a antibody, and particularly a single chain antibody, over a protein antibody *in vivo* as provided by Whittington and Buchsbaum, and the superiority of adenoviral vectors over plasmid vectors for expressing single chain antibodies as taught by Buchsbaum et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to use an adenovirus encoding the anti-IgE antibodies taught by Hardman et al. over the direct administration of the antibodies themselves in order to inhibit IgE binding to IgE receptor *in vivo*. Based on the high level of skill in the art of molecular biology at the time of filing, the skilled artisan would have had a reasonable expectation of success in modifying the adenoviral vectors taught by Whittington et al. or Buchsbaum et al. to include a nucleic acid encoding an anti-IgE antibody as taught by Hardman et al. Furthermore, in view of the teachings of

Buchsbaum et al. and Whittington et al. that adenoviruses encoding an antibody can successfully express therapeutic levels of encoded antibodies in host cells *in vivo*, and the teachings of Hardman et al. that anti-IgE antibodies can be used to inhibit IgE binding to IgE receptors resulting in the treatment of allergic disease, the skilled artisan would have had a reasonable expectation of success in using an adenovirus encoding an anti-IgE antibody to inhibit IgE binding to the high-affinity IgE receptor on cells *in vivo,* thus suppressing or attenuating an IgE related allergic condition.

In response to the previous grounds of rejection under 35 U.S.C. 103(a) over Hardman et al. in view of Buchsbaum et al., the applicant argues that Hardman et al. does not teach *in vivo* methods. However, the rejection above clearly points out that Hardman et al. does teach *in vivo* methods of administering anti-IgE antibody, and that Whittington et al. and Buchsbaum et al. provide motivation for administering an adenovirus encoding antibody over the antibody itself for therapeutic purposes *in vivo*. Furthermore, please note that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7

USPQ2d 1500 (Fed. Cir. 1988). Thus, applicant's arguments regarding the teachings of Hardman et al. are not persuasive in overcoming the instant grounds of rejection.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be

directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit 1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER